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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/618,620	07/15/2003	Jui-Lin Chen	MR2707-37	5660

4586 7590 11/21/2005

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EXAMINER	
MYERS, CARLA J	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 11/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/618,620	CHEN ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-11 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-11 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 22 December 2003 and 15 July 2003 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Specification

1.The specification is objected to because the assigned SEQ ID NOs have not been used to identify each sequence listed, as required under 37 CFR 1.821(d). See Figure 1. The "Brief Description of the Drawings" should be amended to provide the appropriate sequence identifiers for each of the recited sequences or a new Figure 1 should be submitted which includes the appropriate sequence identifiers for each of the recited sequences.

Claim Objections

2. Claims 1 and 11 are objected to because of the following informalities:

In claims 1 and 11 "response" should read "respond."

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-11 are indefinite because the claims do not recite a clear nexus between the preamble of the claims and the final process step of the claims. Claims 1-10 are drawn to a method for detecting the propensity of an individual to respond effectively to treatment with interferon-α and ribavirin therapy. However, the claims recite a final step of analyzing a polynucleotide sample for the presence of a polymorphism in the CD81 gene. The claims do not clarify how the step of detecting the

polymorphism results in the determination of whether an individual has a propensity to effectively respond to said treatment. The claims should be amended to clarify that detection of the polymorphism indicates a propensity of the individual to respond effectively to interferon-α and ribavirin combined therapy. Similarly, claim 11 is indefinite because the claim does not recite a clear nexus between the preamble of the claim of a method for detecting the propensity of an individual to respond effectively to treatment with interferon-α and ribavirin combined therapy and the single process step of the claim of analyzing a haplotype of the CD81 gene and its flanking regions. The claim omits essential process steps because the claim does not clarify how detecting a haplotype results in the determination of whether an individual will respond effectively to treatment with interferon-α and ribavirin therapy.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for detecting a propensity of a HCV-infected human to respond effectively to treatment with interferon-α and ribavirin combined therapy wherein the method comprises detecting the presence of a SNP in the CD81 gene or the presence of a CD81 haplotype and determining that the individual has a propensity to respond effectively to said treatment if said SNP is present, wherein said SNP is selected from the group consisting of T at rs800136, a T at rs800137, a G

at rs800334, an A at pos198603, a T at rs2522012, an A at rs2522013, and a T at rs800335 and wherein the haplotype is a G at rs800136 and a G at rs800137 or the haplotype is TGGCC for the SNPs rs800334, pos1989603, rs252012, rs252013, and rs800335, does not reasonably provide enablement for methods for detecting a propensity of any individual to respond effectively to treatment of interferon-α and ribavirin combined therapy wherein the method comprises detecting the presence of any SNP in the CD81, any CD81 haplotype or any haplotype in a region flanking CD81. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Breadth of the Claims:

The claims are drawn broadly to encompass methods for detecting a propensity of an individual to respond effectively to treatment of interferon-α and ribavirin combined therapy comprising detecting the presence of any SNP in the CD81 gene or any CD81 haplotype or any haplotype of a sequence flanking the CD81 gene. The CD81 genomic

sequence consists of 19,887 bp. The gene is located at 11p15.5 and thereby is flanked by a significant and diverse array of nucleotide sequences, including sequences encoding for TSSC2, IGF2, H19, TSSC4 and KCNQ1. Further, the specification contemplates the detection of any polymorphism or haplotype in a sequence of at least 70 Kb that includes the CD81 gene and 5' and 3' untranslated sequences (see page 35). Accordingly, the claims encompass methods for detecting any polymorphism in the CD81 gene, wherein the polymorphism is not defined in terms of its identity or location. The claims also encompass indirectly by assaying for polymorphisms in linkage disequilibrium with the stated SNPs and any other undefined polymorphisms. The claims further encompass assaying for a haplotype of a CD81 gene or a haplotype of any chromosome 11 sequence. Additionally, the claims encompass predicting responsiveness of any organism to treatment with the interferon-α and ribavirin combined therapy, wherein the organism is being treated to any condition.

Nature of the Invention

The claims encompass methods of predicting effectiveness of therapy for HCV by assaying for the presence of a polymorphism in the CD81 gene. The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

Teachings in the Specification and State of the Art:

The specification (page 15) teaches that the protein level of membrane bound CD81 in isolated peripheral blood cells and hepatocytes is down-regulated in response to treatment with interferon-α alone or in combination with ribavirin. The specification (page 15) states that "it is concluded that interferon-α and ribavirin regulate the expression of CD81 in vitro and in vivo."

The specification provides the results of a study in which 92 Chinese Han patients with chronic HCV infection, treated with a combination of interferon-α and ribavirin therapy were analyzed for the presence of SNPs in the CD81 gene. Nineteen SNPs were detected in the CD81 gene and 7 of these SNPs were found to be associated with response to treatment (see page 32 and Tables 3-14). In particular, the specification teaches an association between effectiveness of interferon-α and ribavirin combination therapy and the presence of the polymorphisms of a T at rs800136, a T at rs800137, a G at rs800334, an A at pos198603, a T at rs2522012, an A at rs2522013, and a T at rs800335. Accordingly, the specification has enabled the detection of each of these 7 SNPS in the CD81 gene as predictive of responsiveness of a HCV-infected patient to treatment with interferon-α and ribavirin combination therapy.

The specification (page 35) states that 9 haplotypes in the 70 Kb region that comprises the CD81 gene have been identified in Figure 17. It is stated that haplotype block 4 and 7 are associated with favorable response to treatment. It appears that "block 4" is intended to refer to a haplotype of G at rs800136 and a G at rs800137. Figure 18 indicates that a haplotype of a C at rs800136 and a C at rs800137 was associated with lack of a favorable response to treatment (responders 46 and non-

responders 52). The TGGCC haplotype for the SNPs rs800334, pos1989603, rs252012, rs252013, and rs800335 was found to be correlated with a favorable response to treatment (page 36, and Figure 19)

The Predictability or Unpredictability of the Art and Degree of Experimentation:

The art of determining an association between a polymorphism and a response to treatment of a disorder is highly unpredictable. Knowledge of the sequence of the wildtype CD81 gene and other sequences and genes flanking the CD81 gene does not allow one to immediately envision specific polymorphisms which are associated with a response to treatment to interferon-α and ribavirin combination therapy. Once a new polymorphism is identified, it remains unpredictable as to whether that polymorphism is present in the general population at levels equivalent to that in HCV-infected individuals that are responsive to treatment with interferon-α and ribavirin.

The specification itself exemplifies the unpredictability in the art of identifying polymorphisms which are associated with a phenotype. While the specification teaches that 19 polymorphisms were identified in the CD81 gene, only 7 of these polymorphisms were found to be associated with response to interferon-α and ribavirin combination therapy. No information is provided in the specification or prior art regarding a mechanistic relationship between the polymorphisms and response to therapy. For example, it is unclear as to how the presence of a T at nucleotide position rs800136 of the CD81 gene effects an individuals responsiveness to treatment with interferon-α and ribavirin. The specification does not teach whether the polymorphisms are located in exon sequences and whether the polymorphisms effect the sequence of the encoded

protein and if so, whether such a change occurs in a region that is important in the binding of HCV particles. Accordingly, there is no predictable means to ascertain a priori whether a polymorphism in the CD81 gene will or will not be associated with response to treatment.

Without extensive information regarding the structure-function relationship between the CD81 gene and flanking gene sequences, it is highly unpredictable as to what would be the identity of additional SNPs, insertions, deletions or splice variants which would be associated with response to interferon-α and ribavirin combination therapy. Thus, one cannot readily anticipate the effect of a polymorphism or mutation within the CD81 gene and flanking sequences.

It is also unpredictable as to whether a polymorphism in the CD81 gene will effect responsiveness to interferon-α and ribavirin treatment in subjects that are not infected with HCV. The specification teaches only the effect of this combined therapy on HCV-infected subjects. There are no teachings in the specification as to how the stated polymorphisms would effect response to treatment in any other types of conditions.

Amount of Direction or Guidance Provided by the Specification:

The specification teaches only 7 SNPS and 2 haplotypes of the CD81 gene which are associated with response to interferon-α and ribavirin treatment. To identify additional polymorphisms in the CD81 gene and in sequences flanking the CD81 gene (and thereby sequences of any region of chromosome 11) which are diagnostic would require extensive experimentation. For example, such experimentation may involve sequencing the CD81 gene and all chromosomal regions of chromosome 11 of affected

individuals that are responsive to treatment with interferon-α and ribavirin, sequencing the CD81 gene and chromosome 11 sequences of control individuals which are not responsive to treatment with interferon-α and ribavirin, comparing the sequences of these two groups, and then identifying polymorphisms which are present only in the group of responders and not in the non-responder group. Such random, trial by error experimentation is considered to be undue.

While methods for identifying polymorphisms are known in the art, such methods provide only the general guidelines that allow researchers to randomly search for polymorphisms that may linked to a phenotype. The results of performing such methodology is highly unpredictable. The specification has provided only an invitation to experiment. The specification does not provide a predictable means for identifying additional polymorphisms and haplotypes of the CD81 gene or flanking sequences using these polymorphisms or haplotypes to identify individuals who will have a favorable response to interferon-α and ribavirin treatment.

Working Examples:

Again, the specification teaches methods for analyzing the nucleic acids of an individual to directly detect the presence of a T at rs800136, a T at rs800137, a G at rs800334, an A at pos198603, a T at rs2522012, an A at rs2522013, and a T at rs800335 or to detect the GG rs800136/rs800137 haplotype or the TGGCC haplotype as defined in Table 17 as indicative that the individual will have an effective response to interferon-α and ribavirin combined treatment. There are no additional examples provided in the specification in which other types of polymorphisms in the CD81 gene or

polymorphisms linked to these SNPs or haplotypes in sequences flanking the CD81 gene are used to determine an individual's response to treatment.

Conclusions:

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

In the instant case, the claims do not bear a reasonable correlation to the scope of enablement because the specification teaches only 7 SNPs and 2 haplotypes of the CD81 gene which are associated with responsiveness to interferon-α and ribavirin treatment. Again, the CD81 gene spans 19.88 kb, yet only 7 nucleotide positions have been identified within the CD81 gene that are correlated with response to therapy. Similarly, the chromosome 11 sequences flanking the CD81 gene encompass hundreds of thousands of additional nucleotide sequences, yet no haplotypes from these regions have been identified which are correlated with response to treatment. Accordingly, the

specification does not teach a representative number of additional polymorphisms, including insertions, deletions, or substitutions in the CD81 gene or a representative number of haplotypes of the CD81 gene or a representative number of haplotypes of sequences which are associated with response to interferon-α and ribavirin treatment.

Further, the specification does not teach each of the novel aspects of the claimed invention because the novelty of the invention lies in the identity of the specific polymorphisms correlated with response of HCV-infected individuals to treatment with interferon-α and ribavirin. The novel aspects of the invention are not methods of identifying additional polymorphisms in the CD81 gene and flanking sequences since general methods of searching for polymorphisms were known in the art at the time the invention was made.

In view of the unpredictability in the art, extensive experimentation would be required to identify additional CD81 polymorphisms and haplotypes which would be associated with response to interferon-α and ribavirin combined treatment. Accordingly, although the level of skill in the art of molecular biology is high, given the lack of disclosure in the specification and in the prior art and the unpredictability of the art, it would require undue experimentation for one of skill in the art to make and use the invention as broadly claimed.

5. Claims 1, 2, 10 and 11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time

the application was filed, had possession of the claimed invention. This is a Written Description rejection.

The claims are drawn broadly to encompass methods for detecting a propensity of an individual to respond effectively to treatment of interferon-α and ribavirin combined therapy comprising detecting the presence of any SNP in the CD81 gene or any CD81 haplotype or any haplotype of a sequence flanking the CD81 gene. The claims do not define the polymorphism or haplotype in terms of the identity of a nucleotide(s) or the location of the polymorphism(s).

The specification teaches an association between responsiveness of HCV-infected patients to treatment with interferon-α and ribavirin and the presence of the CD81 polymorphisms of a T at rs800136, a T at rs800137, a G at rs800334, an A at pos198603, a T at rs2522012, an A at rs2522013, and a T at rs800335 and the CD81 haplotypes of (i) a G at rs800136 and a G at rs800137 and (ii) TGGCC for the SNPs rs800334, pos1989603, rs252012, rs252013, and rs800335. While methods which detect the presence of one of the 7 SNPs or one of the 2 haplotypes meet the written description requirements of 35 U.S.C. 112, first paragraph, the specification does not disclose and fully characterize the genus required by the claims of any polymorphism or haplotype of the CD81 gene or flanking regions that are associated with treatment efficacy of interferon-α and ribavirin combined therapy.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the

'written description' inquiry, whatever is now claimed". Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

In analyzing whether the written description requirement is met for a genus claim, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, 7 polymorphisms and 2 haplotypes of the broadly claimed genus have been identified. No additional polymorphisms or haplotypes are disclosed in the specification or prior art. It is then determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (e.g. restriction map, biological activity of an encoded protein product, etc.). In the instant case, no such identifying characteristics have been provided for any additional CD81 polymorphisms or haplotypes. However, the claims as written are inclusive of a potentially large genus of polymorphisms in the 19.88 kb CD81

gene and in the chromosomal sequences flanking the CD81 gene. While one could contemplate a nucleotide substitution, deletion or addition at each and every position in the CD81 gene and flanking chromosomal sequences, such nucleotide variations are not considered to be equivalent to specific nucleotide variations associated with response to interferon-α and ribavirin therapy. Rather, polymorphisms and haplotypes of the CD81 gene associated with efficacy of interferon-α and ribavirin therapy represent a distinct group of nucleotide variations which are expected to occur at only specific locations within the CD81 gene and consist of specific nucleotide alterations. Accordingly, knowledge of the sequence of the wild-type gene does not allow the skilled artisan to envision all of the contemplated polymorphisms encompassed by the claimed genus. Conception of the claimed invention cannot be achieved until reduction to practice has occurred, regardless of the complexity or simplicity of potential methods for isolating additional nucleotide variations. As stated in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. LTD*, 25 USPQ2d 1016, one cannot describe what one has not conceived.

Further, the specification teaches SNPs of the CD81 gene, but does not teach any other types of polymorphisms in the CD81 gene that are correlated with response to interferon-α and ribavirin therapy. Additionally, the specification does not teach any haplotypes of sequences flanking the CD81 gene that are correlated with response to interferon-α and ribavirin therapy.

Accordingly, the disclosure in the specification of 7 SNPs and 2 haplotypes of the CD81 gene is not considered to constitute a representative number of polymorphisms,

including insertions, deletions, substitutions or splice variants, of the CD81 gene or flanking gene sequences which are associated with efficacy of interferon-α and ribavirin combined therapy. For these reasons, Applicants have not provided sufficient evidence that they were in possession, at the time of filing, of the invention as it is broadly claimed and thus the written description requirement has not been satisfied for the claims as they are broadly written. Applicants attention is drawn to the Guidelines for the Examination of Patent Applications under 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

5. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Kerr et al (Arthritis and Rheumatism. Sept. 1999. 42(9 Supplement) S336, Abstract 1591) teaches a method for detecting a polymorphism in the CD81 gene in patients with HCV infection. Kerr states that CD81 is polymorphic in African American patients and postulates that this may be due to the relative lack of response to response to alpha interferon in these patients. However, Kerr does not teach the identity of the polymorphism and does not teach an association between a CD81 polymorphism and response to interferon-α and ribavirin combined treatment.

Hennig et al (Genes and Immunity. 2002. 3: 359-367) discloses a study in which portions of the CD81 gene were sequenced to screen for polymorphisms in patients infected with hepatitis C virus. Hennig (page 362) reports that "(t)he coding region of the CD81, including exons 5 to 7 which encode the large extracellular loop, was found to be

highly conserved in the 35 patients sequenced, indicating that novel polymorphisms were not present in this region."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (571) 272-0747. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571)-272-0745.

The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866)-217-9197 (toll-free).

Carla Myers
November 9, 2005

Carla Myers
CARLA J. MYERS
PRIMARY EXAMINER